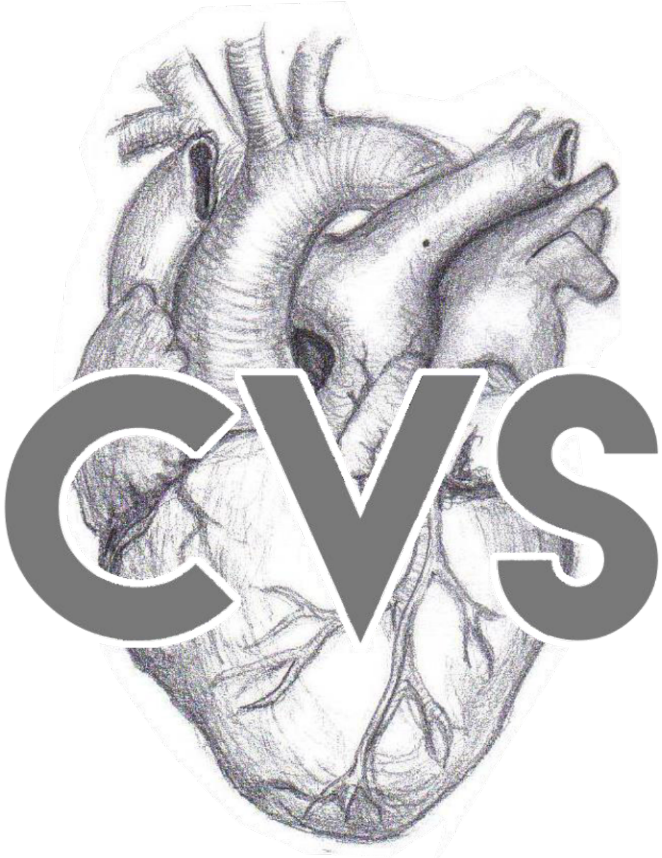

PHARMACOLOGY

☑ Sheet ○ Slide ○ Handout

Number

9

Subject

Mechanisms of Cardiac Arrhythmias

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Date: **00/00/2016**

Price:

Effects of K+

Don't always assume that the effect of K+ is related to its electrochemical gradient. sometimes it's related to its electrochemical gradient and u can understand its effect by this gradient effect but if it's not >> u have to simply memorize it , so don't think a lot about K+ effects , a lot of its effects cannot be explained.

Effects of hypokalemia

knowing that K+ is mainly responsible for phase 3 of cardiac AP "repolarization phase" during this phase K+ efflux is predominant (the cell become more –ve as it losses positive charges) when there's hypokalemia >> this phase will be affected >> the exit of K+ will be reduced and the cell will spend extra time in "depolarization phase">> **prolonging the AP**.
when the AP becomes longer >> the refractory period prolong too>> this make the AP susceptible to develop "**early after-depolarization**" –will be discussed later- but if this early after-depolarization reaches the threshold it is going to fire another AP >> abnormal beat >> arrhythmia.

So we can conclude that hypokalemia is **arrhythmogenic** , and it must be corrected before using any anti-arrhythmia drug >> as hypokalemia will make their action less.
in fact correcting hypokalemia is very effective to the extance that if u just correct it the arrhythmia may disappear without the need for anti-arrhythmia drug.

Also hypokalemia make the AP susceptible to develop "**delayed after-depolarization**" which happen at rest phase "the baseline "during diastole due to Ca++ overload.
Note : this effect cannot be explained.
hypokalemia **increase pacemaker rate**, recall that the pacemaker rate depends on the spontaneous depolarization "phase4" K+ do contribute in this phase by making the cell more –ve "as it effluxes out ", when there's hypokalemia the cell

become more +ve and subsequently it will reach the threshold faster >> the rate increase.

Effects of hyperkalemia

hyperkalemia effects are the opposite of hypokalemia effects, it will reduce the AP duration as phase3 will become sharp and fast , and this will shorten the systole>> shorten the AP.
it will reduce the HR and so on, u can read the next 3 slides now.
remember : excessive decrease in HR may develop cardiac arrest. ”block in AV node will make the atria and the ventricles contract separately.
according to the Dr in the US they use lethal injection in some executions , these injections contain K>> they cause hyperkalemia >> cardiac arrest.

Effects of K^+

- **The effects of changes in serum potassium on cardiac action potential duration, pacemaker rate, and arrhythmias may look paradoxical if we consider only potassium electrochemical gradient.**

Hyperkalemia:

1. **Reduces AP duration.**
2. **Slows conduction.**
3. **Decreases pacemaker rate.**
4. **Decreases pacemaker arrhythmogenesis.**

- **Thus, both insufficient and excess potassium is potentially arrhythmogenic.**
- **Therefore, potassium therapy is directed toward normalizing potassium gradients and pools in the body.**

Hypokalemia:

1. **Prolongs AP duration → increased risk of early- and delayed- afterdepolarizations.**
2. **Increases pacemaker rate.**
3. **Increases pacemaker arrhythmogenesis, especially in the presence of digitalis.**
4. **Increases arrhythmogenicity of antiarrhythmic drugs (accentuated action potential prolongation and tendency to cause torsades de pointes).**

- **Effects more on ectopic pacemakers than SA node.**

Mechanisms of Cardiac Arrhythmias

Factors that precipitate or exacerbate arrhythmias:

1. **Hypoxia or Ischemia.**
2. **Acidosis or alkalosis.**
3. **Electrolyte abnormalities.**
4. **Excessive catecholamine exposure.**
5. **Other autonomic influences.**
6. **Overstretching of cardiac fibers.**
7. **Scarred or diseased tissue.**
8. **Drug toxicity: Digitalis and antiarrhythmic drugs.**

Explinations and comments :
#1 ischemia of the heart (local hypoxia at the heart). Remmeber in MI there's focal dead T surrounded by ischemic tissue surrounded by normal T. the ischemic T is the one susceptible for arrhythmia >> in fact this the cause of sudden death after MI infraction (generalized MI can cause sudden death too).
#2 acid-base imbalance reflected on many things on the body. (we will take it with renal system)
#3 electrolytes abnormalities, specially Na+ , Ca++ , K+ & Mg++. (Mg++ is similar to K+ and opposite to Ca++)
#4 excessive catecholamine exposure= sympathetic stimulation , when excess it will cause tachycardia (extra-systoles)
#5 other autonomic influences >> specially the parasympathetic >> reduce the HR and conduction through the AV node.

remember . We consider both tachycardia and bradycardia >> arrhythmogenic if they were excessive to the extent that they needed Treatment.

#6 overstretching of the cardiac fibers , when this happen acutely >> this mean that the heart has failed.
#7 scarred tissue = fibrous Tissues interrupting normal cardiac Tissue >> interrupting conduction.
diseased Tisseues = ischemic.
arrhythmogenic drugs : digitalis and anti-arrhythmogenic drugs
ALL ANTI-ARRHYTHMIA DRUGS ARE ARRHTHMOGENIC WITHOUT EXCEPTIONS.
why ?
these drugs are of narrow therapeutic index , meaning that when they produce an effect (to reverse arrhythmia) if this effect was exasperated a little bit >> they will produce arrhythmia. –as here we are dealing with ions –both hypo or hyper state of these ions can produce arrhythmia.

Mechanisms of Cardiac Arrhythmias

Disturbances in cardiac rhythm result from:

1. **Disturbances in impulse formation.**
2. **Disturbances in impulse conduction.**
3. **Disturbances in both.**

Impairment of impulse formation

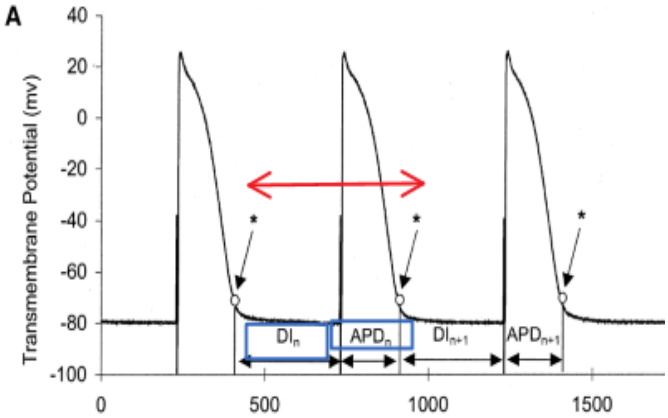
The heart rate = number of beats in min
each beat = Action potential duration + length of diastole (diastole interval)
if any of these two become shorter the beat will become shorter

if any of these two become longer the beat will be prolong

Tuesday, November 15, 2016 6:13 PM

Disturbances in impulse formation

- **The interval between depolarizations of a pacemaker cell is the sum of the duration of the action potential and the duration of the diastolic interval.**
- **Shortening of either duration results in an increase in pacemaker rate.**
- **The diastolic interval, is determined primarily by the slope of phase 4 depolarization (pacemaker potential).**

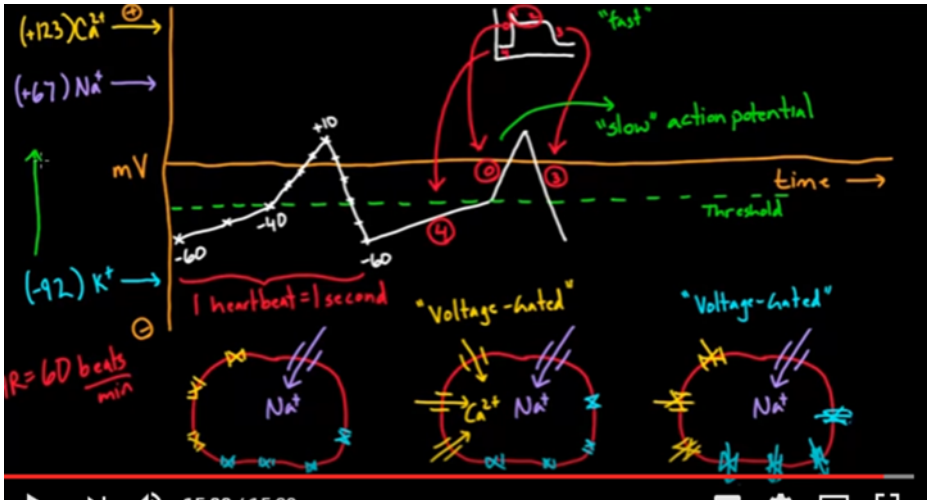


The length of diastole is determined by the duration of diastolic depolarization in phase 4 in the conducting tissue. (which can be observed as the slope of phase 4)

vegal discharge (parasympathatic) decrease the HR by decraesing phase 4 slope>> decreasing diastolic length>> it needs longer time to reach the threshold.

If the HR become accelerated increase the slope >> we reach the threshold earlier.
acctually this is the mechansim in which the overstretching ,ishcemia , acid-base imbalance …will produce arrhythmia by.

DI = Diastolic interval = phase4 which is dependent on the funny current (I_f)which itself is determined by K+ efflux
when there is hypoK+ (say induced by sympathetic stimulation) the rate increase and the slope of phase 4 increase
when there is hyperK+ (parasympathetic stimuli) the rate decrease and the slope of phase 4 decrease
Why ?
as said before K+ determine the funny current Na flow.
when there's hyperK+ the AP is driven toward the
(AP of the cell if it was preamble to K alone "diffusion potential of K" which is -92)
ie. The cell potential become more -ve >> it needs more time to reach the threshold >> the rate become less.
why the slope decrease ?
[I THINK] when the membrane is more permeabile to K+ it become harder for the Na+ (of the funny current) to neutralize and then overcome K+ effect>> acts slower>> the slope decreases.



I've tried to put extra-explanitions here *were not mention by the doctor

1. **Vagal discharge and β-receptor-blocking drugs slow normal pacemaker rate by reducing the phase 4 slope (acetylcholine also makes the maximum diastolic potential more negative).**

- **Acceleration of pacemaker discharge may be produced by increased phase 4 depolarization slope, which can be caused by hypokalemia, β-adrenoceptor stimulation, positive chronotropic drugs, fiber stretch, acidosis, and partial depolarization by currents of injury, which especially affects Purkinje fibers latent pacemakers.**

Early Vs delayed after depolarization

What are these?

Afterdepolarizations are transient depolarizations that interrupt phase 3 (early afterdepolarizations, EADs) or phase 4 (delayed afterdepolarizations, DADs).

EADs are usually exacerbated at slow heart rates and are thought to contribute to the development of long QT-related arrhythmias.

- **DADs, on the other hand, often occur when intracellular calcium is increased.**
- **They are exacerbated by fast heart rates and are thought to be responsible for some arrhythmias related to digitalis excess, to catecholamines, and to myocardial ischemia.**

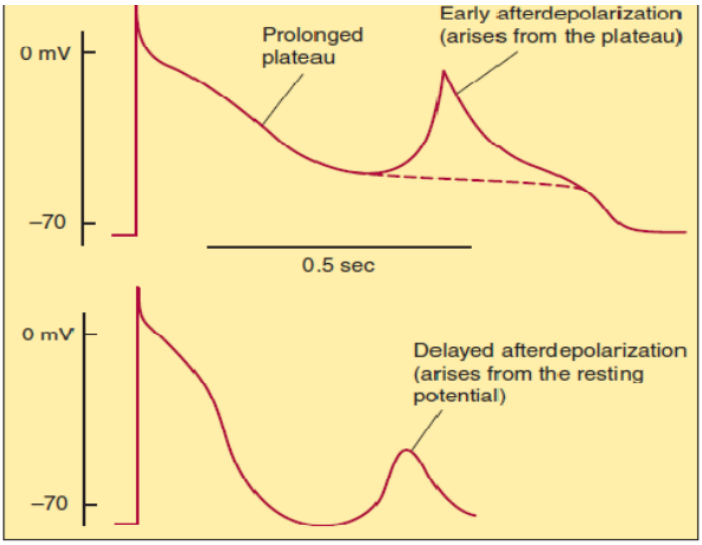


FIGURE 14–5 Two forms of abnormal activity, early (**top**) and delayed afterdepolarizations (**bottom**). In both cases, abnormal depolarizations arise during or after a normally evoked action potential. They are therefore often referred to as "triggered" automaticity; that is, they require a normal action potential for their initiation.

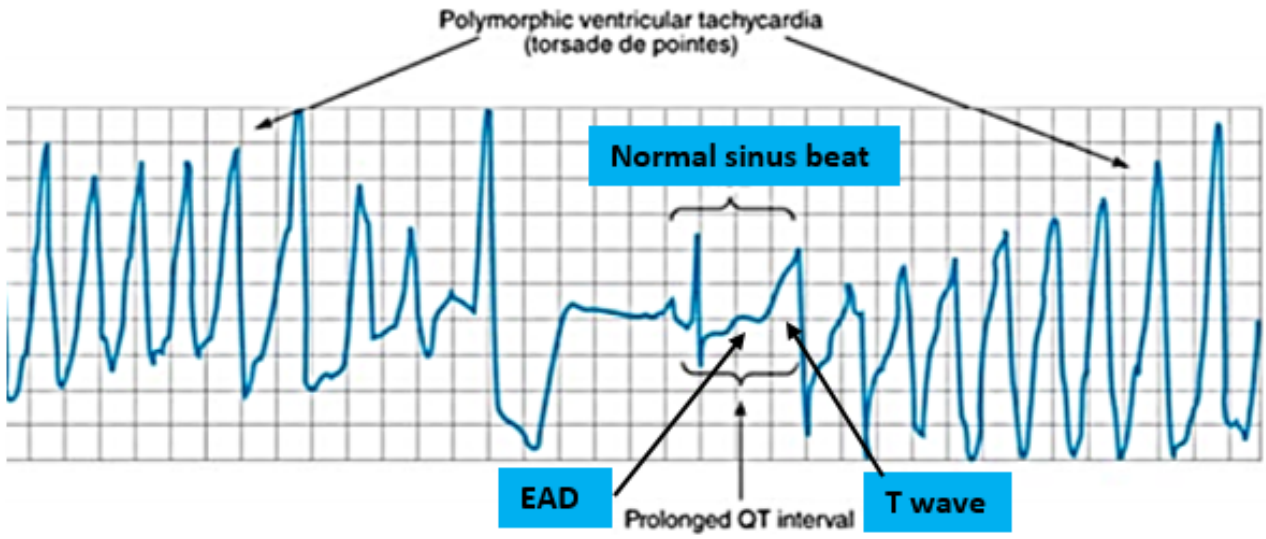
In EAD , the refractor is gone away, if EAD reach the threshold >> it will does extra systole will be produced. This abnormal beat is usally stronger than the normal ones >> that's why u feel like "وقع قلبي"

If EAD was sustained>> a lot of extra-systoles >> tachycardia or arrhythmia.
Note we can tolerate up to 4 extra systoles in min- without the need for Tx.(normal)

Torsades de pointes (polymorphic ventricular tachycardia/ long QT syndrome)

an emergency in which QRS complexes of the ECG become polymorphic (different in amplitude and shape) it can turn into ventricular fibrillation .
it's most likely that torsades de pointes arise from EAD which also implies disturbances in T wave too.

this fig. represent the ECG of torsades de pointes notice how two episodes of polymorphic tachycardia are separated by a single normal sinus beat >> what is abnormal about this beat that its QT interval is longer >> here the EAD beat can arise.
remember : we can observe EAD on the AP curve and ECG diagram.



Any drug interfere with phase-3 can produce torsade de pointes . also hypokalemia produce it.

The polymorphic ventricular tachycardia known as torsades de pointes is associated with prolongation of the QT interval, syncope, and sudden death.

This represents prolongation of the action potential of some ventricular cells.

The effect can be attributed to either increased inward current (gain of function) or decreased outward current (loss of function) during the plateau of the AP.

Mutations in ions channels and Torsades de pointes :

These mutations can be loss or gain of function mutations.

Gain of function mutation for K+ channel (more active)>> AP duration lower.
loss of function mutations of K+ channels (less active)>> AP duration longer >> can produce Torsades de pointes.
Gain of function of Na+ and Ca++ channels also prolong the duration of AP.

- **Loss-of-function mutations in potassium channel genes produce decreases in outward repolarizing current and can cause LQT.**
- **Gain-of-function mutations in the sodium channel gene or calcium channel gene cause increases in inward plateau current and also cause LQT.**
- **Thus, therapy is directed at correcting hypokalemia, eliminating triggered upstrokes (by using β blockers or magnesium), or shortening the action potential (by increasing heart rate with isoproterenol or pacing), or all of these.**
- **The potassium channel I_{kr} is blocked or modified by many drugs (quinidine, sotalol) or electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia) that also produce torsades de pointes.**
- **It is likely that torsades de pointes originates from triggered upstrokes arising from early after-depolarizations.**

Short QT syndrome

Might be associated with gain of function mutations in some K+ channels genes>> phase 3 more acute>> shorter.

Catecholaminergic polymorphic ventricular tachycardia

As u know ER (sarcoplasmic reticulum of cardiac muscles) have Ca++ channels on. these channels are sensitive to catecholamines (=sympathetic stimulation , which can be triggered by stress) when these channels are mutated catecholamines effects on them can produce polymorphic ventricular tachycardia.

4. **Short QT syndrome may be linked to gain-of-function mutations in some potassium channel genes.**
5. **Catecholaminergic polymorphic ventricular tachycardia, a disease that is characterized by stress or emotion-induced syncope, can be caused by genetic mutations in two different proteins in the sarcoplasmic reticulum that control intracellular calcium homeostasis.**

Now we've finished disturbances in impulse formation .

disturbances in impulse conduction

✓ AV block

the conduction pathway normally (SA>> AV node>> AV bundle>> His- purkinje system.

If AV is delayed this will produce heart block. As if the AV conduction is slow >> the next impulse that reach the AV from the SA will not excite it -as it will be in its refractory->> this make the atrial rate different from ventricular rate.
Note: atrial fibrillation is less important than ventricular fibrillation as 75% of blood filling the ventricles pass through the atria passively.

Treatment of AV block ,
when thinking about HR and AV conduction we must consider the parasympathetic as the main controller. The parasympathetic predominantly control HR by reducing it . it controls the atria only –with its conduction system : SA node & AV node) .
in AV block we want to increase the conduction rate of AV so we shut down the parasympathetic effect by using atropine.

atropine:

1) Increase HR
2) Increase conduction velocity

3) Decrease refractory period in AV

Now read this slide:

- **Severe depression of conduction may result in block (AV- block or bundle-branch block)**
- **Partial AV block is reversed by atropine because parasympathetic control of AV conduction is significant.**

✓ Re-entry (circus movement)

The same impulse that stimulate one area of the heart will get back (by a circus route) to excite this area again (back to point of origin).
if this impulse circulate once it gives us one extra systole –abnormal-

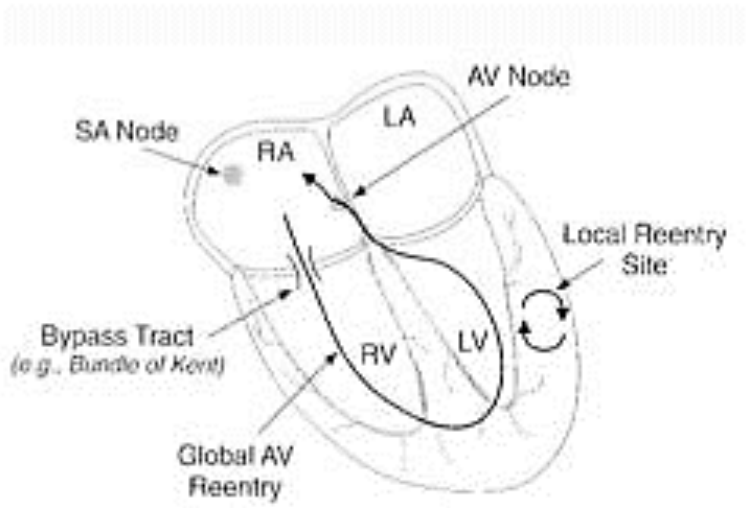
If this impulse circulates for a lot of times –doesn't die- and become sustained >> it will produce arrhythmia.

One of the congenital re-entry circuit is present at Wolf-Parkinson-White Syndrome who have extra bundle (bundle of Kent) between Atria and ventricles (it is a bypass for the AV node and bundle) .
this extra bundle is fast conducting fibers (its AP is Na+ dependent)
while the original bundle is slow conducting fibers (its AP is Ca++ dependent)
Note : both SA and AV conduction system are Ca++ dependent >> slow conductors
while his- purkinje system are Na+ dependent >> this makes them fast conductors.

Now , the circus movement can involve small or large area of the heart.
in Wolf-Parkinson-White Syndrome ,bundle of Kent involve large area >> between the Atria and the ventricles, also SA and AV system is included.

When SA node create a beat it will go to AV but remember Normally AV always delay the impulse passage to ventricles to confirm that the systole of V does not begins unless the A systole ends>> but in this syndrome we have extra-fast conduction that will allow the "SA-waiting-beat" to be conducted bypassing the

AV.
- here we can consider the AV bundle as a physiological/anatomical obstacle. this kind of physiological obstacle is due to slow conduction and tissue long refractory.



We can have mechanical obstacle like fibrosis within the conduction tissue itself. this can happen as result of ischemia.

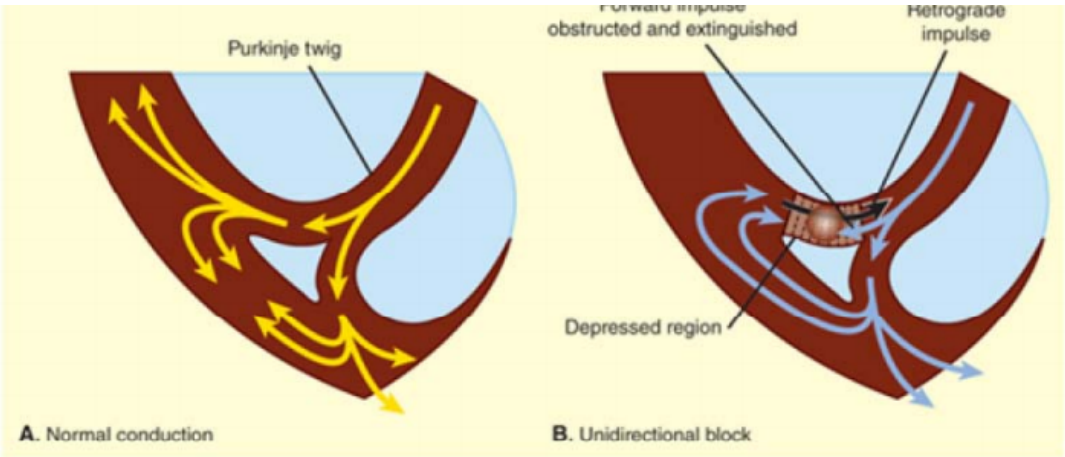
Mechanisms and conditions for re-entry:
his- purkinje system is full with bifurcation >> which aids in propagation of impulses.
this make things more complicated and more susceptible to produce re-entries (as these conduction fibers are fast – and they exit their refractories fast >> they are almost always ready for a next excitatory impulse)

Now these 3 conditions for re-entry must make sense for u:

In order for reentry to occur, 3 conditions must coexist:

1. **There must be an obstacle to homogeneous conduction – anatomic or physiologic – thus establishing a circuit around which the re-enterant wave front can propagate.**
2. **There must be unidirectional block at some point in the circuit, i.e. conduction must die out in one direction but continue in the opposite direction.**
3. **Conduction time around the circuit must be long enough so that retrograde impulse does not enter refractory tissue as it travels around the obstacle (conduction time must exceed the ERP).**

Look at this image and read its key



Source: Bertram G. Katzung, Anthony J. Trevor: Basic & Clinical Pharmacology, 13th Ed.
www.accesspharmacy.com

Figure 14-6: Schematic diagram of a reentry circuit that might occur in small bifurcating branches of the Purkinje system where they enter the ventricular wall.
A: Normally, electrical excitation branches around the circuit, is transmitted to the ventricular branches, and becomes extinguished at the other end of the circuit due to collision of impulses.
B: An area of unidirectional block develops in one of the branches, preventing anterograde impulse transmission at the site of block, but the retrograde impulse may be propagated through the site of block if the impulse finds excitable tissue; that is, the refractory period is shorter than the conduction time. This impulse then reexcites tissue it had previously passed through, and a reentry arrhythmia is established.

Notice in the abnormal block (B)
there's a black arrow through-out the fibrous tissue >>how come the impulse can pass this site ?

Simply the impulse finds away – even if it was micro- bypassing the obstacle and get back to its site of origin (and complete the circle).
also the Dr said that these impulses are so fast to the extinct that they can jump over the obstacle (imagine them as "need for speed" cars when the car is so fast >> it can fly bypassing a Roadless area or in case of impulses a conduct-less area.
look at the figure .

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